II. REMARKS

FORMAL MATTERS

Claims 1, 6, 8-9, 25-28, 30, 36-37, 53, and 56-66 were pending prior to entry of the above amendment.

Claims 26, 53, and 64-66 are hereby canceled without prejudice or disclaimer.

Claims 67-68 are newly added.

Claims 1, 8, 9, 25, 27-28, 30, 36, 37, 56-61 are hereby amended to clarify aspects of the claimed invention and resolve antecedent basis issues.

Support for the amended and newly added claims can be found in at least paragraphs [0003], [0040], [0044], [0079], and [0090]-[0097], and Tables 1, 2 and 4 of the specification, and the original claims as filed.

Accordingly, claims 1, 6, 8-9, 25, 27-28, 30, 36-37, 56-63, and 67-68 are now pending, with claims 56-63 pending, but withdrawn from consideration. It is noted that new claim 68 may be deemed withdrawn in view of its dependency upon claim 56, which is presently withdrawn.

Claims 56-63 and Claims 1 and 25 are independent. The remaining claims depend, directly or indirectly, from independent claims 1 and 25.

No new matter is added.

INTERVIEW SUMMARY

Applicants wish to express their gratitude to Examiners Woitach and Qian (by telephone) for the in-person interview with Craig Wilde, Kathleen Determann, and the undersigned on October 7, 2008. The rejections of the present action were discussed during the interview, and claim amendments substantially as set out herein were discussed. Applicants have reviewed the Interview Summary dated October 16, 2008, and agree with the Examiner as to the substance of the interview.

RESTRICTION REQUIREMENT

Applicants thank the Examiner for acknowledging that claims 56-63 will be rejoined upon allowance of claims 1 and 25. Applicants request that the Examiner acknowledge that new

claim 68, which depends directly from withdrawn claim 56 and indirectly from claim 1, will also be rejoined upon allowance of claim 1.

Claims 65 and 66 have been withdrawn from consideration as being directed to a non-elected invention. However, as these claims have been canceled, this restriction requirement is moot and Applicants respectfully ask that it be withdrawn.

REJECTIONS UNDER 35 USC § 112

Claims 1, 6, 8, 9, 25-28, 30, 36, 37, 53, and 64 stand rejected under 35 USC § 112, first paragraph, as "failing to comply with the enablement requirement." (*See*, OA at p. 3.) Claims 26, 53, and 64 have been canceled, therefore the rejection to these claims is moot and Applicants respectfully request that it be withdrawn. To the extent that this rejection also applies to amended claims 1, 6, 8, 9, 25, 27-28, 30, and 36-37, Applicants respectfully traverse it.

To be enabled, the specification must describe the invention in such terms that one skilled in the art can make and use the invention. MPEP § 2164. Not everything necessary to practice the invention need be disclosed. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. MPEP § 2164.08. Thus, the enablement requirement is met if the specification enables one mode of making the invention. *Johns Hopkins Univ. v. CellPro, Inc.,* 152 F.3d 1342, 1361 (Fed. Cir. 1998). An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. MPEP § 2164.06.

Breadth of claim, teaching of specification, degree of experimentation

Mere presence of mRNA

The Examiner has interpreted the claims as encompassing a method for predicting breast cancer recurrence "by the mere presence of MYBL2 expression of both mRNA and protein." (*See*, OA at p. 4, 7.) However, amended claims 1 and 25, upon which the other claims depend, directly or indirectly, describe a method comprising assaying an expression level of an RNA transcript of MYBL2, or its expression product, and normalizing that expression level, wherein the normalized expression level of the MYBL2 transcript, or its expression product, positively

correlates with the likelihood of breast cancer recurrence in the patient. The Examiner has conceded that the specification establishes "a correlation between breast cancer recurrence or death and the higher expression of the mRNA transcripts of the sequence disclosed in NM_002466." (*See*, OA at p. 4-5, 7.) Applicants agree that such a correlation *is* established in the specification as filed.

The specification provides data from an example in which a t test assuming equality of variance was performed on the groups of patients classified as either having no recurrence and no breast cancer related death at three years, versus recurrence, or breast cancer-related death at three years, and the p-values for the difference in mean expression between the groups. (*See*, Specification at paragraphs [0090]-[0099].) Table 1 lists 47 genes for which the p-value for differences between the groups in mean expression was less than 0.10. The first column of mean expression values pertains to patients who neither had a metastatic recurrence of, nor died from, breast cancer. The second column of mean expression values pertains to patients who either had a metastatic recurrence of, or died from, breast cancer.

Similarly, Tables 2 and 3 present results for the subsets of ER positive and negative patients. In Table 2 there are 57 patients with normalized CT for estrogen receptor ER > 0 (i.e. ER positive patients). A t test was performed on the two groups of patients classified as either no recurrence or no breast cancer related death at three years, or recurrence or breast cancer related death at three years, and p-values for the differences between the groups for each gene were calculated. The first column of mean expression values pertains to patients who neither had a metastatic recurrence nor died from breast cancer. The second column of mean expression values pertains to patients who either had a metastatic recurrence of or died from breast cancer. Table 2 lists genes where the p-value for the differences between groups was less than 0.1 . (*See*, *also*, Specification at paragraphs [0095]-[0098].) The resulting t-tests provide evidence of a statistically significant difference in mean normalized expression measurement between patients with breast cancer recurrence and patients without breast cancer recurrence. These results are indicative of a significant association of gene expression with likelihood of breast cancer recurrence.

The ordinarily skilled artisan would recognize that the data in the tables in the specification may be used to construct a curve showing a positive correlation of MYBL2 normalized gene expression values and increasing likelihood of breast cancer recurrence. For

example, the ordinarily skilled artisan can apply logistic regression analysis to model the probability of breast cancer recurrence as a function of gene expression measurement (C_T). For example, Appendix A provides results from logistic regression analysis for recurrence or breast cancer related death at three years, respectively, for the corresponding genes provided in Table 2. Results reveal that, as expected, the resulting p-values from the likelihood ratio tests of significance of gene expression measurement under the logistic model are very close to the p-values generated by the corresponding t-tests. (*See, e.g.*, Specification at paragraphs [0100]-[0107].)

Appendix B provides a predicted probability plot of recurrence or breast cancer related death at 3 years, for ER positive patients, as a function of MYBL2 expression along with 95% confidence intervals. The "Estimate" number for MYBL2 from Appendix A represents the slope of the curve in Appendix B, and "AUC" (App. A) the curve inflection point. Logistic regression analysis may be used to relate data, including the "Odds Ratio" and "Estimate" from Appendix A, to determine predictive probability of response. Thus, the specification illustrates that the greater the normalized MYBL2 expression values, the worse the prognosis for breast cancer patients.

Thus, the specification provides sufficient details to allow one skilled in the art to predict the likelihood breast cancer recurrence or death based on expression levels of MBYL2.

Correlation at the protein level

The Examiner has taken the position that "the specification does not teach whether this correlation is also observed at protein level." (*See*, OA at p. 5, 7.) As a general rule, however, a correlation between RNA levels and protein expression is known in the art. *See, e.g., Amgen v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1298 (Fed. Cir. 2006). Members of the MYB family proteins have been found to perfectly correlate with corresponding mRNA levels. (*See, e.g.*, Lacoste, et al., British Journal of Haematology, 138:487-501 (2007) (MYB expression in lymphoma cells) (Exhibit A). Absent evidence to the contrary, the ordinary artisan would reasonably expect that mRNA levels in cancer would correlate to the levels of associated protein(s). *Ex part Lee*, 2008 WL 447537 (BPAI 2008): ("As the Examiner has not provided any evidence to dispute the reasonably calculated correlation between…mRNA levels and [associated] protein levels, the rejection cannot be sustained.")

Orthologs and splice variants

The Examiner also indicates that MYBL2 refers to myeloblastosis oncogene-like 2 as well as "orthologs wherein the sequences are substantially different from each other … and splice variants which may exist, but their full-length nature have not been determined." (*See*, OA at p. 4.) However, the enablement requirement allows for a reasonable amount of experimentation to determine if an invention is applicable to splice variants. *US v. Telectronics*, 857 F.2d 778 (Fed. Cir. 1988).

The MYBL2 gene is identified in the specification using the Genbank accession no., NM_002466, defined therein as Homo sapiens v-myb myeloblastosis viral oncogene homolog (avian)-like 2. According to the annotated summary by the NCBI staff, "[t]ranscript variants **may** exist for this gene, but their full-length natures have not been determined." (Emphasis added.) Thus, there is currently no definitive evidence that splice variants existed at the time the application was filed. The Examiner has provided no evidence to the contrary.

Nonetheless, even if the existence of MYBL2 splice variants *were* confirmed in the future, the specification would still be sufficient to allow one skilled in the art to determine which sequences would be associated with likelihood of breast cancer recurrence. For example, using the amplicon sequence provided in Table 5A of the specification, one could simply conduct a BLAST search to determine which of the isoforms would have been measured using the disclosed invention. Therefore, it would require only a reasonable amount of experimentation to confirm which MYBL2 sequences were amplified in the examples provided in the specification, and to design probe/primers to amplify a conserved region.

State of the art

The Examiner takes the position that "the prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test." (*See*, OA at p. 7.) However, Applicants respectfully assert that the references cited (OA, p. 5-7) do not establish a reasonable basis to question the enablement provided for the claimed invention. MPEP § 2164.05. First, references to literature concerning the predictability of disease diagnostics[1] are inapposite as the

[1] The post-filing references, Kroese, et al., Genetics in Medicine, Vol. 6:475-480 (2004), and Lucentini, et al., The Scientist, p. 20 (Dec. 20, 2004) both concern studies correlating gene expression with disease states. (*See*, OA at p. 10.)

claimed method involves patients who have independently been diagnosed with breast cancer. (*See, e.g.*, Specification, paragraphs [0010] and [0082].)

Second, the references concerning gene profiling actually teach that validated assays supported by statistically meaningful data are reliable. For example, Shalon et al. (US 2001/0051344 A1, Dec. 13, 2001) (hereinafter "Shalon") indicate that when differences in expression "persist in comparison of the averaged gene expression patterns from [two populations], it becomes more likely that the expression of that particular gene is related to the shared phenotype of the test individuals…Standard statistical analyses may be applied to determine when the messenger nucleic acids from a sufficient number of individuals [at least 5] have been evaluated for differences in gene expression." (Shalon at paragraphs [0155]-[0156].) Similarly, other references cited by the Examiner support the powerful potential of gene expression profiling that, like the instant invention, is clinically validated[2] and incorporates reproducible quality control.[3]

Finally, the application as filed provides evidence of the association of normalized MYBL2 gene expression levels and breast cancer recurrence. As noted above, the specification includes data in Tables 1, 2, and 3 that provides evidence of a statistically significant difference in mean normalized expression measurement between patients with breast cancer recurrence and patients without breast cancer recurrence for MYBL2. These results are indicative of a significant association of normalized expression of MYBL2 with increased likelihood of breast cancer recurrence.

In view of the above, Applicants respectfully assert that the Examiner has failed to present evidence that the specification, at the time filed, would not have taught one skilled in the art how to make and/or use the full scope of the amended claims without undue experimentation. MPEP § 2164.01(a). Therefore, Applicants respectfully request that the rejection be withdrawn.

Claim 30

The Examiner indicates that "the specification does not teach what sort of treatment is recommended based on the expression of MYBL2." (*See*, OA at p.4, 7.) Amended claim 30 describes identifying a treatment option for the patient based on the normalized expression level of MYBL2. Where different arts are involved in the invention, the specification is enabling if it

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[2] Murphy, et al., Pathology, 37(4):271-277 (2005).

enables persons skilled in each are to carry out the aspect of the invention applicable to their specialty. MPEP § 2164.05(b). In this case, the information provided by the claimed method would help inform a treatment recommendation by a medical professional based on the current standard of care. (*See*, Specification at paragraph [0003].) For example, in breast cancer, treatment recommendations are available from the National Comprehensive Cancer Network and the American Society of Clinical Oncology.

For these reasons, Applicants respectfully assert that amended claim 30 is supported by the specification, and request that this rejection be withdrawn.

Claim 53

The Examiner indicates that "the specification does not teach how the reference control cancer sample is chosen." (*See*, OA at p. 7.) As claim 53 has been canceled, this rejection is moot. Applicants respectfully request that the rejection be withdrawn.

[3] Koree, et al., Current Pharmacogenomics, Vol. 3:201-216 (2005).

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GHDX-008.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 2, 2008

By: /Carol L. Francis, Reg.No.36513/
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Enclosures:
Appendices A and B
Exhibit 1: Lacoste, et al., British Journal of Haematology, 138:487-501 (2007)

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